NH₄Br – Br₂ Catalysed Oxidative Bromination of Aromatic Compounds

Sushil Kumar Sharma  
PhD research Scholar  
Department of Chemistry  
JJTU Rajasthan

Prof. D.D Agarwal  
Ex-Vice Chancellor JJTU Rajasthan

Abstract
A facile, efficient, simple, environmentally safe, regioselective, controllable and economical method for the oxybromination of aromatic compounds using NH₄Br-Br₂ system. The electrophilic substitution of bromine generated in situ from NH₄Br as a bromine source and molecular bromine as an oxidant.

Keywords: Halogenation, Oxidative bromination, Molecular bromine, Aqueous medium

Introduction
Previous studies of organic transformation shows, organic ammonium bromides are becoming a small yet important group of reagents. Because of their ease of formation, mildness, immense versatility, these reagents have become quite popular and a number of reports are available discussing the importance of these reagents in various types of transformations. The effects of pH, electrolyte, and surface preparation on the surface excess and adsorption kinetics are reported. At all other concentrations and even at the Critical Surface Aggregation Concentration when electrolyte is present, the adsorption is complete within minutes.

Halogenated organic compounds form an important class of intermediates as they can be converted efficiently into other functionality by simple chemical transformations. The manufacture of a range of bulk and fine chemicals including flame retardants, disinfectants and antibacterial and antiviral drugs, involve bromination. Bromo aromatics are widely used as intermediates in the manufacture of pharmaceuticals, agrochemicals and other specialty chemical products. Selective bromination of aromatic compounds is investigated in view of the importance of the brominated compounds in organic synthesis. Consequently, a variety of methods for the bromination of aromatics have been reported in the literature.

Brominated aromatic compounds are widely used as building blocks for pharmaceuticals, and other specialty chemicals. Most of the aromatic compounds are poorly soluble in water, and this has been a major limitation in the preparation of industrially-important brominated compounds under aqueous conditions. Classical nuclear bromination of aromatic compounds involves the use of: (a) Bromine; (b) A catalyst like FeCl₃, FeBr₃, iodine, thallium acetate etc; (c) Absence of light, often yielding undesired Co-products. The direct bromination of an aromatic system presents an environmental problem in large-scale operations. Besides, the bromination is wasteful as one half ends up as hydrogen bromide and this renders the process more expensive. Oxybromination using HBr is highly toxic and corrosive and is as harmful as molecular bromine to the environment.

Cerichelli et al. studied the bromination of anilines in aqueous suspension of 1-hexadecylpyridinium tribromide (CPyBr₃). The drawbacks include an additional step for the formation of tribromide reagent prior to bromination, complex workup procedure in which brominated product was extracted using diethyl ether and that molecular bromine is required for the preparation of tribromide. Currie et al. have performed the bromination of phenols and anilines in a dodecyltrimethylammonium bromide (DTAB) based microemulsion. The process uses excess amount of hazardous HNO₃ and volatile halogenated organic solvent (CH₂Cl₂). Firouzabadi et al. have disclosed a double catalytic system for the bromination of phenol derivatives using Br₂/Cetyltrimethylammonium bromide (CTAB)/Tungstophosphoric acid cesium salt (Cs₂₂H₉₅PW₁₂O₄₀) reagent system.
The drawbacks are the use of excess amount of reagent (Br₂: substrate, 1.1:1 for mono- and 2.2:1 for dibromination) and expensive halogenated organic solvent is cumbersome during large scale operations.

The reported methods on bromination of aromatic compounds in water are rare and limited to only few examples such as NaBr-H₂O₂/scCO₂ biphasic system and H₂O₂-HBr”on water” system, albeit low conversions, high temperature (40 °C) and a very long reaction time (from 8 h to 28 h ) are some of the concomitant shortcomings. There are also some other reagents that have been developed as a substitute for Br₂, including, but not limited to, N-bromosuccinimide/1-butyl-3-methylimidazolium bromide, ZrBr₄/diazene, [K. 18-crown-6]Br₃, 1-butyl-3-methylpyridinium tribromide [BMPy]Br₃, 3-methylimidazolium tribromide [Hmim]Br₃, 1-butyl-3-methylimidazolium tribromide [Bmim]Br₃ pentylypyridinium tribromide, ethylene bis(N-methylimidazol) ditribromide. However, no such reagent is commercialized to date, because of their expensive nature, poor recovery and recycling of spent reagent, disposal of large amounts of HBr waste and that the reagents are also not so stable and weaken during long periods of storage, hence that are meant only for laboratory-scale preparations with limited applications. Preparation of all these reagents involve liquid bromine at some stage, thereby, increases the cost of the end-product. All the above reported methods suffer from using not easily available compounds and others use highly-corrosive or expensive reagents and toxic organic solvents. Examples are: Br₂/Ag₂SO₄, Br₂/SbF₅/HF, Br₂/SOCl₂/Zeolite, Br₂/Zeolite, Br₂/H₂O₂, Br₂/H₂O/Layered Double Hydroxide-WO₄, Br₂/tetrabutylammonium peroxydisulphate etc. Therefore, the bromination reaction has been still attracting attention to develop the more practical method suitable for industrial-scale synthesis. These observations enhance the versatility of bromine as an inexpensive, readily available starting material. A wide range of solvents have been employed in these reaction including, carbon tetrachloride, hexane, methanol, acetonitrile, and acetic acid.

**Scheme 1.** Ammonium bromide catalyzed oxibromination of aromatic compounds in water using molecular Br₂

\[
\text{NH}_4\text{Br} + \text{Br}_2 \rightarrow \text{NH}_4\text{Br}_3 + \text{Br}^-
\]

\[
\text{NH}_4\text{Br}_3 + \text{Br}^- \rightarrow \text{NH}_4\text{Br}_3 + \text{Br}^-
\]

\[
\text{Y = OH, NH}_2, \text{NHCOMe, NHCOPh, CHO, COOH}
\]

\[
\text{X = OH, NO}_2, \text{SO}_2, \text{NH}_2
\]

**Objective**

In the face of demands for sustainable and ecologically-friendly organic synthesis, clean organic reaction processes which do not use harmful organic solvents are encouraged and are in great demand today. The direct bromination of aromatic compounds with molecular bromine in solution often results in polybromination, and when brominated in the presence of oxidants, they also get oxidized rather than undergoing substitution. Although bromination of aromatic compounds by elemental bromine is a well-known organic reaction, bromination using elemental bromine usually results in a complex mixture of mono-, di-, tri-, and even tetra-brominated products. Hence to date, there has been no simple, inexpensive, instant, easily available, and high yield method developed that can be commercialized for the said purpose. A variety of new bromination techniques have been employed along with the conventional reagent “bromine” to increase the efficiency and selectivity. Still, the use of toxic and expensive reagents, catalysts, VO₃S, low yields and discharge of corroding HBr waste circumvent these processes from industrial application. Oxybromination, on the other hand, can be a good alternative. yet these reactions require a great excess of the reagents, strongly acidic conditions, expensive dangerous pollutant to the environment. Alternative analogues of bromine such as organic tribromides and various tribromide-ionic liquids have also been used for the bromination of aromatic compounds. Nevertheless, these brominating agents are saddled with various drawback including their low atom economy, disposal of toxic and corrosive HBr byproduct waste, poor recycling of spent reagent, and the molecular bromine required for their preparation.
Hence, to eliminate a two-step bromination wherein these reagents are first prepared using molecular bromine prior to bromination of aromatic compounds, we have effectively utilized molecular bromine at the first place along with an environmental-friendly reagent NH\textsubscript{4}Br for an instant and facile bromination for industrially important compounds. Due to the above reasons, molecular bromine is still a target alternative for industrial chemists to develop an environmental-friendly brominating system which works under ambient conditions, keeping this in mind, we find an aq NH\textsubscript{4}Br-Br\textsubscript{2} system to be a better alternative.

**Experimental Section**

**Materials and Methods**

Analytical reagent grade starting material and reagents were obtained from commercial suppliers and were used without further purification. Granular and scaly substrates were grinded in mortar and converted into fine powder prior to reactions. Doubly distilled water was used all through the study. HPLC analyses were conducted using waters 2695 instrument with PDA detector, column C\textsubscript{18} (250 mm x 4.6 mm x 5 \(\mu\)m), solvent system 70\% CH\textsubscript{3}OH + 30\% H\textsubscript{2}O, flow rate 1 ml/min. HPL purity is reported by area%. NMR spectra were obtained in DMSO and CDCl\textsubscript{3} on a Bruker Avance ll 400 NMR spectrometer, the chemical shifts were reported in \(\delta\) ppm, \(^1\)H NMR (relative to TMS referenced as 0.00 ppm) and \(^{13}\)C NMR (relative to DMSO referenced as 39.50 ppm). GC/MS analyses were carried out using Agilent GC (Model 5893) with Chemstation software; column-HP5-MS, 30 m x 0.25 mm x 0.25 micron; detector temp-30ºC; injection volume-1 microliter of 5\% solution in methanol. Mass spectre were recorded on Micromass Quattro Micro API triple quadrupole MS equipped with a standard APCI ion source. IR spectra were recorded on a Bruker Avance ll 400 NMR spectrometer, the chemical shifts were reported in \(\delta\) ppm, \(^1\)H NMR (relative to TMS referenced as 0.00 ppm) and \(^{13}\)C NMR (relative to DMSO referenced as 39.50 ppm). GC/MS analyses were carried out using Agilent GC (Model 5893) with Chemstation software; column-HP5-MS, 30 m x 0.25 mm x 0.25 micron; detector temp-30ºC; injection volume-1 microliter of 5\% solution in methanol. Mass spectre were recorded on Micromass Quattro Micro API triple quadrupole MS equipped with a standard APCI ion source. IR spectra were recorded on a Shimazu Prestige 21 FT-IR Spectrometer (KBr, 3500-440 cm\(^{-1}\)). The yields were calculated by weight.

**Typical procedure for the synthesis of 3,5-Dibromosalicylic acid (1)**

To a mixture of salicylic acid (1.38g, 10 mL SLS micellar solution at its CMC (8.1 X 10\(^{-3}\) m) was added bromine (3.2 g, 20 mmol) utilizing a pressure-equilizing funnel and the resulting mixture was stirred at room temperature. The bromine colour disappeared at once and white thick precipitates of 3,5-dibromosalicylic acid were obtained within 5 min (monitored by TLC) of reaction time at 25ºC. After 15 min, the precipitated reaction mass was separated from mother liquor by vacuum filtration and then washed with Na\textsubscript{2}S\textsubscript{2}O\textsubscript{5} solution (10\%, 10 ml x 3) and dried in oven at 100ºC to get white crystalline powder of 3,5-dibromosalicylic acid. The total isolated yield was 2.902 g (98.06\%) with an HPLC purity of 99.3\%. The characteristic data recorded for the isolated product were mp 226-229ºC (lit.\(^4\) 225-229ºC); \(^1\)H NMR (400 MHz, DMSO): \(\delta\)7.79 (d, 1H, J=2.4 Hz, ArH), 7.94(d, 1H, J=2.4 Hz, ArH), 10.36 (s, 1H, OH), 12.04 (s, 1H, COOH); \(^{13}\)C NMR (100 MHz, DMSO): 170.65, 157.20, 139.67, 131.54, 115.01, 111.29, 109.71; IR(KBr): 3215, 3092, 3057, 2839, 2583, 2519, 1663, 1595, 1452, 1425, 1385, 1300, 1274, 1150, 1130, 876, 789, 714, 681, 658, 600, 552, 471 cm\(^{-1}\); MS m/z calcd. for C\textsubscript{13}H\textsubscript{8}Br\textsubscript{2}O\textsubscript{5}: 305.9, FOUND 305.8.

**Recycling of HBr**

Molecular bromine carries significant industrial advantages, including low price, low favourable E-factors\(^14\) and high productivity. This last factor (the amount of substance produced per unit reactor volume per unit time) which is often ignored in laboratory studies, is crucial in all large-scale processing. As these advantages of Br\textsubscript{2} cannot be matched by other bromine sources. Viable industrial oxybromination reagents must feature alternative benefits. The aqueous filtrate obtained after the separation of bromination product was neutralized by adding Ca(OH)\textsubscript{2} (0.7409 g, 10 mmol). Initially, the pH of the aqueous filtrate was <3. When Ca(OH)\textsubscript{2} was added in small lots to the aqueous filtrate, the Br\textsubscript{2} of HBr was transformed into CaBr\textsubscript{2} (at Ph 7). After the separation of CLS (22.6 mg), the aqueous mixture thus obtained containing CaBr\textsubscript{2} was concentrated to precipitate CaBr\textsubscript{2} (1.997 g) as a crystalline solid.

**Results and Discussion**

Our initial exploratory studies probed the best reaction conditions and for that we choose salicylic acid (10 mmol) as a typical compound which was first reacted with molecular bromine (20 mmol) in CH\textsubscript{3}CN (10 ML) at room temperature for 50 minutes. Workup of the reaction resulted under-brominated off-white 3,5-dibromosalicylic acid (3,5-DBSA) which melts over a range 190-221 ºC (Table 1, entry 1).
Other solvents such as CH₃COOH, CH₃OH, CAN, H₂O and CH₃Cl₂ were also tested but the results were unsatisfactory, yielding 3,5-dibromosalicylic acid in lower yields with low melting points where the crude product is contaminated by significant quantities of impurities particularly the monobrominated salicylic acid or decarboxylated brominated phenol.

**Table 1: Optimization of Reaction Conditions for the Bromination of Salicylic Acid (10 Mmol) Using Molecular Bromine (20 Mmol) to Afford 3,5-Dibromosalicylic Acid**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagent System</th>
<th>Reaction Condition</th>
<th>Yield (%)</th>
<th>Mp/°C(lit. 225-229°C)</th>
<th>Appearance</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Br₂/CH₃CN⁶</td>
<td>50 min at rt</td>
<td>87</td>
<td>190-221</td>
<td>Off-white granular powder</td>
</tr>
<tr>
<td>2.</td>
<td>Br₂/CH₃CN/H₂O⁷</td>
<td>60 min at rt</td>
<td>89</td>
<td>200-220</td>
<td>Off-white powder</td>
</tr>
<tr>
<td>3.</td>
<td>Br₂/CH₃CN/NH₄Br/H₂O⁸</td>
<td>25 min at rt</td>
<td>94</td>
<td>221-228</td>
<td>White crystals</td>
</tr>
<tr>
<td>4.</td>
<td>Br₂/NH₄Br/H₂O⁹</td>
<td>20 min at rt</td>
<td>92</td>
<td>221-223</td>
<td>White crystals</td>
</tr>
<tr>
<td>5.</td>
<td>Br₂/NH₄Br/H₂O¹⁰</td>
<td>15 min at rt</td>
<td>96</td>
<td>226-229</td>
<td>White-shining crystals</td>
</tr>
<tr>
<td>6.</td>
<td>Br₂/H₂O¹¹</td>
<td>65 min at rt</td>
<td>83¹²</td>
<td>190-200</td>
<td>Off-white granules</td>
</tr>
</tbody>
</table>

Yield of isolated end-product  
Reaction conditions: CH₃CN 10 ml  
Reaction conditions: CH₃CN 10 ml, H₂O 5 ml  
Reaction conditions: NH₄Br 5 mg, CH₃CN 10 ML, H₂O 5 ml  
Reaction conditions: NH₄Br 5 mg, H₂O 10 ml  
Reaction conditions: NH₄Br 23mg, H₂O 10 ml  
Underbrominted product was obtained.

Then we carried out the above reaction in CH₃CN-H₂O mixture (2/1 by volume) under same reaction conditions. The results show that 3,5-DBSA was synthesized in fair yield but the mixture, color and melting point of the product were not within the required standards (the melting point should be >225 °C and appearance should be white-crystalline as per international standards). The presence of water during the reaction dramatically affects the solubility of the desired 3,5-DBSA, causing it to precipitate immediately upon formation. Next, we performed the bromination of salicylic acid (10 mmol) with molecular Br₂ (20 mmol) in CH₃CN (10 ml) by adding aqueous solution of NH₄Br (5 mg in 5 ml water) into the reaction media at room temperature. This reaction proceeded well and the bromine color disappeared immediately resulting an instantaneous synthesis of 3,5-DBSA within 25 min of reaction time. The product was obtained in 94% yield with a melting point 221-228 °C. This reaction has cleared that the reactivity of bromine can be enhanced in aqueous reaction media. Then we decided to run the above reaction in the absence of CH₃CN under the same conditions. The workup yielded the product in almost same yield (89%) but the melting point was slightly dipressed (Table 1, entry 4). We observed an immediate disappearance of redish-brown color in the flask and whole of the bromine get consumed within 2-3 minutes of stirring indicating that an instant interaction between the bromine and aromatic substrate has occurred in the aqueous catalytic system. White-shining crystalline powder of 3,5-DBSA was obtained in 96% yield (HPLC purity was 98.3%) having melting point 226-229 °C (Table 1, entry 5).

Since we had observed large increase in the ring bromination rate using NH₄Br-Br₂ system, we decided to study the behavior of aromatics in order to determine whether the NH₄Br-Br₂ system could achieve ring bromination without competition from benzylic bromination. Moreover, electrophilic aromatic bromination which involves the ionization of bromine-ring charge transfer-complex is extremely fast in aqueous media in which the formation of the bromonium ion is strongly assisted by electrophilic solvation of the leaving bromide ion (scheme 3).
Scheme 3: Bromination transition state

It is assumed that molecular bromine oxidizes the Br(NH₄)Br to Br⁺, which reacts in the presence of bronsted acid with organic substrate to give brominated compounds.

Effect of nature of ammonium bromide on the yield and melting point of 3,5-DBSA

Table 2 clearly indicates that anionic micelles accelerate the rate of bromination; cationic micelles inhibit bromination while non-ionic micelles show no appreciable effect on the bromination of salicylic acid. Using SLS at its CMC, white-shining crystals of 3,5-DBSA were obtained in 96% yield having melting point 226-229 °C with an HPLC purity of 98.8% that also conform to the required standards of pharmaceutical grade 3,5-DBSA.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Parameter</th>
<th>Ammonium bromide</th>
<th>CTAB</th>
<th>Triton X-100 (TX-100)</th>
<th>International standard</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Appearance</td>
<td>White-crystalline powder</td>
<td>White-grayish powder</td>
<td>White-powder</td>
<td>White crystal</td>
</tr>
<tr>
<td>2</td>
<td>Melting point (°C)</td>
<td>226-229</td>
<td>200-223</td>
<td>212-225</td>
<td>&gt;225</td>
</tr>
<tr>
<td>3</td>
<td>HPLC purity (%)</td>
<td>98.6</td>
<td>94.9</td>
<td>96.2</td>
<td>99 minimum</td>
</tr>
<tr>
<td>4</td>
<td>Yield (%)</td>
<td>96</td>
<td>83</td>
<td>91</td>
<td>98 maximum</td>
</tr>
</tbody>
</table>

*Reaction conditions: Salicylic acid 10 mmol, Br₂ 20 mmol, NH₄Br 23 mg, CTAB 3.35 mg, TX-100 15 mg, water 10 ml, temp 25±1 °C, time 15 min

Cationic micelles produced less-brominated 3,5-DBSA in poor color and yield and the reaction was accompanied with the evolution of bromine fumes which makes the handling of the reaction for the large-scale operation uneasy. Triton X-100, however, improves the color and purity of 3,5-DBSA but the yield and melting point were comparatively low. The higher rate of bromination in anionic as compared with cationic micelles was ascribed to a favorable interaction of the incipient bromonium ion (Br⁺) with the anionic sulphate head group and unfavorably with a cationic head group. The slow reaction in CTAB was ascribed to the formation of less reactive tribromide ion as the cationic micelles strongly modify both the Br₂/Br⁻ equilibrium towards the formation of tribromide ion. The inhibition of the reaction by cationic micelles in water was explains on the basis that Br₃⁻ (the only brominating agent assumed to be in the micellar phase) is 5-6 orders of magnitude less reactive than Br₂⁻ and in presence of cationic micelles of CTAB, we can assume that Br₂⁻ is virtually completely in the Br₃⁻ form.

Effect of amount of ammonium salt on the yield and melting point of 3,5-DBSA

The quantity of ammonium salt plays a key role in the quality of product. The optimum yield (96 %) and the desired melting point (226-229 °C) of 3,5-DBSA are obtained when 23 mg of NH₄Br was employed in the bromination of salicylic acid (10 mmol) using molecular Br₂ (20 mmol) as a brominating agent. At 5 mg and 10 mg of NH₄Br, the yield of 3,5-DBSA were 91 and 93% respectively. If we increase the amount of NH₄Br upto 50 mg and 100 mg, there is no marked effect on the yield, melting point and quality of the product.

To investigate the scope of present bromination method, we, therefore, applied similar reaction conditions to a variety of phenol and aniline derivatives with strong electron-withdrawing groups such as carboxylic, nitro and formyl as examples of pharmaceutical intermediates (Table 3). The different aromatic substrates brominated may have different solubilization sites in the micellar aggregate as indicated by their log P values. However, in the present system the rate of reaction is very fast and the lipophilicity of aromatic substrate does not play any significant role. The consumption of bromine in the reaction is immediate and most of the reactions are completed within 10-15 min of reaction time followed by the addition of bromine into the round-bottom flask, affording the brominated products in >99 HPLC purity.

Acetanilide 2 and benzanilide 3 were efficiently brominated to their corresponding para-brominated products in excellent yields. This indicates that the position of the electrophilic attack as well as the number of entering bromine atoms can be regulated by controlling the ratio of Br₂⁻ substrate, i.e. 1:1 for mono-, 2:1 for di- and 3:1 for tribromination of aromatic compounds.
Conventional bromination using molecular bromine in organic solvent or concentrated HBr is not very selective and often results in a complex mixture of mono-, di-, tri-, and even tetra-brominated products. 2,4,6-Tribromoaniline (table 3, entry 4), an intermediate for agrochemicals and pharmaceuticals, and 2,4,6-tribromophenol (table 3, entry 9), a reactive flame retardant were obtained in good yields utilizing 3 molar equivalents of molecular Br₂. 1-Naphthol 6 and 2-napthol 7 proceeded with good reactivity affording clean synthesis of 2,4-dibromo-1-naphthol (93%) and 1,6-dibromo-2-naphthol (91%) after 15 minutes, respectively. It has been found that sulphanilamide 8 and oxine 9 could also be instantaneously dibrominated affording 3,5-dibromosulphanilamide and 5,7-dibromooxine (a potent antifungal and antiamoebic) in yields of 97 and 99%, respectively. Pharmaceutically-important aromatic aldehydes were instantaneously brominated at room temperature in excellent yields (table 3, entries 6, 7 and 15). Another anthelminic or antibacterial, 2,4-dibromo-6-nitrophenol was obtained in excellent yield within 20 min from 2-nitrophenol (table 3, entry 11). The bromination of 2-nitrophenol is difficult using binary catalytic system (Br₂/CTAB/Cs₂⁵H₀⁵PW₁₂O₄₀). The regioselective bromination of anilines containing deactivated groups is not an easy task and in most of the methods, it proceeded under harsh reaction conditions with low yields.

**Table 3: Bromination of Various Aromatics with Molecular Br₂ in Nh₄br at Room Temp.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Time/min</th>
<th>Yield (%)</th>
<th>Mp/°C (lit.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>NHCOCH₃</td>
<td>Br-NHCOCH₃</td>
<td>10</td>
<td>98</td>
<td>167(165-169)</td>
</tr>
<tr>
<td>2.</td>
<td>NHCOPh</td>
<td>Br-NHCOPh</td>
<td>25</td>
<td>92</td>
<td>200(200-202)</td>
</tr>
<tr>
<td>3.</td>
<td>OH</td>
<td>Br-OH</td>
<td>15</td>
<td>93</td>
<td>105(105-107)</td>
</tr>
<tr>
<td>4.</td>
<td>O</td>
<td>Br-OH</td>
<td>20</td>
<td>95</td>
<td>104(105-107)</td>
</tr>
<tr>
<td>5.</td>
<td>H₂N-Br-SO₂NH₂</td>
<td>Br-H₂N-Br-SO₂NH₂</td>
<td>20</td>
<td>95</td>
<td>235(235-237)</td>
</tr>
<tr>
<td>6.</td>
<td>CHO</td>
<td>Br-CHO</td>
<td>15</td>
<td>96</td>
<td>80(80-84)</td>
</tr>
<tr>
<td>7.</td>
<td>HO-CHO</td>
<td>Br-HO-CHO</td>
<td>20</td>
<td>90</td>
<td>183(181-185)</td>
</tr>
</tbody>
</table>
8. | ![Image](https://example.com/image8) | ![Image](https://example.com/image9) | 15 | 98 | 200(198-200)  
9. | ![Image](https://example.com/image10) | ![Image](https://example.com/image11) | 15 | 91 | 92(92-94)  
10. | ![Image](https://example.com/image12) | ![Image](https://example.com/image13) | 25 | 93 | 120(120-121)  
11. | ![Image](https://example.com/image14) | ![Image](https://example.com/image15) | 20 | 95 | 114(116-117)  
12. | ![Image](https://example.com/image16) | ![Image](https://example.com/image17) | 15 | 94 | 108(110-113)  
13. | ![Image](https://example.com/image18) | ![Image](https://example.com/image19) | 20 | 97 | 127(127-130)  
14. | ![Image](https://example.com/image20) | ![Image](https://example.com/image21) | 20 | 96 | 102(100-103)  
15. | ![Image](https://example.com/image22) | ![Image](https://example.com/image23) | 15 | 92 | 166(164-166)  
16. | ![Image](https://example.com/image24) | ![Image](https://example.com/image25) | 15 | 90 | 102(102-104)  
17. | ![Image](https://example.com/image26) | ![Image](https://example.com/image27) | 20 | 94 | 204-208 (206-208)

*Confirmed by comparison with authentic samples. All reactions were carried out on 10 mmol scale, Br₂ 10 mmol (for mono-), 20 mmol (for di-) and 30 mmol (for tribromination), NH₄Br 23 mg, water 10 mL, temp 25±1 °C  
*Yield of isolated pure product
The absence of organic solvent in reaction enabled simple isolation procedure comprised of filtration of solid brominated product and the aqueous liquid mixture thus obtained containing HBr by product was neutralized by adding powered Ca(OH)$_2$. Since the present method avoided the use of any expensive brominating agents, organic solvents, strong acids; hazardous oxidants and metal catalysts, and operates completely in water, it seemed valuable to extend this system for the bromination of other industrially-important compounds. Scaling-up of the reaction should not give any significant problem for the micellar route because of the rapid and facile bromination and easy to handle workup procedure.

Figure 1: LC-MS of 3, 5-Dibromosalicylic Acid (1)
Figure 2: $^1$H and $^{13}$C-NMR Spectra of 3, 5-Dibromosalicylic Acid (1)
Figure 3: $^1$H and $^{13}$C-NMR Spectra of 3, 5-Dibromosalicylic Acid (1)
Figure 4: IR Spectra of 3, 5-Dibromosalicylic Acid (1)

Figure 5: $^1$H-NMR Spectra of 2, 4, 6-Tribromoaniline (4)
Figure 6: $^1$H-NMR Spectra of 5, 7-Dibromooxine (9)

Figure 7: $^1$H-NMR Spectra of 3, 5-Dibromosalicyldehyde (10)
Figure 8: GC-MS Spectra of 3, 5-Dibromosalicyldehyde (10)
Conclusions

In an effort to eliminate the use of toxic and expensive organic solvents used in conventional bromination techniques, we have exploited the aqueous solution of NH4Br for a fast synthesis of industrially-important brominated compounds quantitatively and qualitatively under ambient conditions using inexpensive molecular Br2 as a brominating agent. This method proceeded purely in water providing a new procedure for the synthesis of brominated compounds of industrial importance. A comparison of the brominating ability of the present system with those of published methods shows that the present protocol is inexpensive, simpler, faster and more efficient than other catalytic bromination systems used for this purpose. The present method which is more attractive than the earlier methods, offers the additional advantages such as the commercial availability of the reagent, simple reaction conditions, no evolution of HBr, high yield, economical easy setup and workup, selective monobromination with high regioselectivity, inexpensive, and environmentally friendly process makes our method valuable from preparative point of view.

Spectral data (1H NMR, IR and MS) of of brominated compounds is given below:

4-bromoacetonilide (2): White crystals; 1H NMR (400 MHz, DMSO): δ 2.1 (3H, s), 7.25 (2H, d, J= 8.4 Hz), 7.52 (2H, d, J = 8.8 Hz), 9.73 (1H, s); IR (KBr): 3293, 3260, 3186, 3115, 3052, 1668, 1644, 1601, 1586, 1532, 1487, 1394, 1309, 1290, 1255, 1007, 831, 819, 740, 687, 504 cm⁻¹; MS m/z calcd. for C8H8BrNO: 216.07, FOUND 216.4.

4-Bromobenzanilide (3): Light grayish powder; 1H NMR (400 MHz, CDCl3): δ 7.29-7.74 (9H, m); IR (KBr) : 3339, 3054, 1661, 1589, 1411, 1196, 946, 893, 750, 714, 509 cm⁻¹; MS m/z calcd. for C13H10BrNO: 276.132, FOUND 276.

2,4,6-Tribromoaniline (4): White shining fine needles; 1H NMR (400 MHz, CDCl3): δ 7.49 (s, 2H, ArH), 5.21 (bs, 2H, NH2); IR (KBr): 3414, 3293, 1452, 1383, 1285, 1225, 1063, 858, 729, 706, 673, 546, 486 cm⁻¹; MS m/z calcd. for C6H4Br3n: 329.816, found 327.

2,4-Dibromo-1-naphthol (6): Grayish-brown powder; 13C NMR (100 MHz, CDCl3): 148.02, 131.73, 130.93, 127.97, 126.97, 126.74, 124.92, 122.66, 113.27, 103.09; IR (KBr): 3412, 3075, 1961, 1934, 1720, 1616, 1583, 1548, 1502, 1449, 1374, 1330, 1266, 1230, 1209, 1146, 1057, 1030, 966, 870, 851, 766, 716, 671, 646, 602, 580 cm⁻¹; MS m/z calcd. for C10H6Br2O: 302, found 300.
1,6-Dibromo-2-napthol (7): Light brown solid; $^1$H NMR (400 MHz, CDCl₃): δ 6.20 (1 H, brs), 7.40-7.78 (2H, dd, J=66 and 9 Hz), 8.15-8.36 (2H, dd, J=33 and 9 Hz), 8.76 (1H, s); IR (KBr): 3485, 3444, 1617, 1586, 1381, 1210, 1183, 928, 871, 805, 645, 536, 512 cm⁻¹.

5,7-Dibromo-8-hydroxyquinoline (9): Light beige powder; $^1$H NMR (400 MHz, DMSO): δ 8.90 (dd, 1H, arom), 8.46 (dd, 1H, arom), 7.89 (s, 1H, arom) 7.65 (t, 1H, arom); IR (KBr): 3071, 1738, 1583, 1491, 1459, 1389, 1333, 1273, 1210, 1183, 922 | 797, 695, 575, 532, 457 cm⁻¹.

2,6-Dibromo-4-nitroaniline (18): Yellow powder; $^1$H NMR (400 MHz, DMSO): δ 8.21 (2H, s), 6.79 (1H, s); IR(KBr): 3485, 3444, 1617, 1586, 1381, 1333, 1273, 1210, 1183, 922 | 797, 695, 575, 532, 457 cm⁻¹; MS m/z calcd. for C₇H₂Br₂NO: 295.9, found 295.2.

5. References


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